REMARKS

Applicants have amended the claims to more particularly define the invention taking into consideration the outstanding Official Action. The claims have been amended to overcome the claim objection set forth in the Official Action with respect to the names of microorganisms which need to be italicized.

The rejection of newly submitted claims 11-16, 18-27 and 29-36 under 35 U.S.C. 103 as unpatentable over Youmans et al. in view of Schroder has been carefully considered but is most respectfully traversed for the reasons set forth in the previous response and the following reasons.

These claims have been rejected on the basis that the Examiner finds that it would have been prima facie obvious to add the monoglyceride preparation as taught by Schroder to the *Mycobacterium tuberculosis* vaccine of Youmans et al.

Applicants again note the requirements for a prima facie case of obviousness as set forth in the MPEP § 2143 as discussed in the previous response. Section 2143.03 states that all claim limitations must be taught or suggested by the prior art. In re Royka, 490 F.2d 981, 180 USPQ 580 (CCPA 1974). "All words in a claim must be considered in judging the patentability of that claim against the prior art." In re Wilson, 424 F.2d 1382, 1385, 165 USPQ 494, 496 (CCPA 1970). If an independent claim is nonobvious under 35 U.S.C. 103, then any claim depending therefrom is nonobvious. In re Fine, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988). In this regard, the Examiner attention is direct to the limitation in the claims that the immunizing component is **inactivated *Mycobacterium tuberculosis* bacteria**. This is a claim limitation which cannot be ignored.

Applicants also most respectfully again direct the Examiner's attention to MPEP § 2144.08 (page 2100-114) wherein it is stated that Office personnel should consider all rebuttal argument and evidence present by applicant and the citation of In re Soni for error in not considering evidence presented in the specification. In this regard, the

Examiner's attention is most respectfully directed to example 1 in Applicants' specification which clearly establishes the patentability of the claimed subject matter.

As previously noted, the problem to be addressed by the presently claimed invention is the formulation of an improved TB vaccine.

Even though the prior art of Schroder suggests an adjuvant for use in a vaccine formulation, it does not suggest a TB vaccine. The only examples mentioned in patent application by Schroder are vaccines comprising diphtheria toxoid, influenza virus, and rotavirus.

According to the Examiner, Youmans et al. teaches a tuberculosis vaccine comprising heat or chemically killed *Mycobacterium tuberculosis*.

The paper by Youmans et al. contains a comparison between tuberculosis vaccine comprising either viable attenuated cells or heat or chemically killed cell. The results shown clearly states that living cells prove to be several hundred times more effective as immunizing agents against tuberculous infection than autoclaved cells or cells inactivate by chemical agents. Actually, in the conclusion (p. 112, column 2, last sentence) is stated that living and killed mycobacterial cells differ not only quantitatively in their capacity to immunize against tuberculous infection, but qualitatively as well, the living cells being far more effective as immunizing agents.

Thus, there is no indication that a TB vaccine comprising inactivated *Mycobacterium tuberculosis* would be especially effective.

Furthermore, page 111, 2 column in Youmans et al. reads:

"There is little indication from the data that immunizing activity of whole cells, whether viable or killed, was affected appreciably by being administered in Fruend's incomplete adjuvant".

Since the paper clearly describes very little, if any, success in administering the *M. tuberculosis* cells together with adjuvant, it certainly does not render it obvious to produce a TB vaccine composition as described and claimed in the present application comprising whole cell *M. tuberculosis* together with an adjuvant.

Applicants believe the teaching of the known prior art by Schroder and Youmans neither taken alone nor in combination provide any hint to use the adjuvants of Schroder in the formulation of a TB vaccine comprising **inactivated** *M. tuberculosis* cells or the success of this vaccine. In re Fritch, 23 USPQ 1780, 1784(Fed Cir. 1992) ("It is impermissible to engage in hindsight reconstruction of the claimed invention, using the applicant's structure as a template and selecting elements from references to fill the gaps.). Accordingly, it is most respectfully requested that this rejection be withdrawn.

From the results of the study performed by Youmans et al a person skilled in the art will recognize the importance of using living attenuated mycobacterial cells for immunizing against tuberculosis infection. Thus, Youmans et al describe that *"The data clearly show that the response to immunization with both living and heat-killed cells is dose-dependent and that living cells are several hundred times more effective than heat-killed cells"* (see page 109, first column, lines 1-5 from the bottom). This finding has been used in standard vaccination programs against Tuberculosis for many years and as seen from a transcript from FDA's homepage www.fda.gov, the TB vaccines on the US market contain live BCG. The same applies also in European countries such as, e.g. in Denmark, where a vaccine against TB (tuberculosis) (BCG Vaccine "SSI") presently on the market contains freeze-dried living attenuated bacteria from Calmette Guerin.

Furthermore, Youmans et al teach that an adjuvant like Freund's adjuvant does not have any improving effect on the immune response irrespective of whether the adjuvant is used together with living or heat-killed mycobacterial cells. Accordingly, a person skilled in the art would realize that the important issue in connection with provoking an immune response against M. Tuberculosis would be to use living cells and that the use of an adjuvant would not have any impact on the result.

Schroder (1997) teaches the use of an adjuvant for stimulating the immune response, but there is no mention that such an adjuvant would be suitable for use also in situations where Freund's adjuvant has no effect or a negative effect on the immune response (e.g. such as in connection with viable or heat-killed cells from M. tuberculosis, cf. Youmans et al.). Accordingly, Applicants most respectfully submit that a person

skilled in the art would based on the combined teachings in Youmans et al. and in Schroder and faced with the intention of developing an improved TB vaccine arrive at the conclusion **that living cells were of vital importance in this respect** and that it would be most unlikely that an adjuvant would be able to improve the immune response significantly. Accordingly, there would be no motivation of a person skilled in the art to try the adjuvant described by Schroder in order to improve a TB vaccine.

Even if a person skilled in the art would try, the teaching of Youmans et al and Schroder in combination would lead the skilled person to a vaccine composition containing living cells of M. tuberculosis (cf. Youmans et al) together with the adjuvant of Schroder due to the fact that Youmans et al have shown that inactivated (heat-killed) cells of M. tuberculosis do not lead to a suitable result.

In contrast hereto, the present invention claims the use of inactivated Mycobacterium tuberculosis bacteria. **From the examples included in the specification** it is demonstrated that it is important that the bacteria are inactivated. Thus, Example 1 describes the results using two different BCGs, namely heat-killed BCG in two different adjuvant formulations and live BCG. From fig. 1 it is seen that the heat-killed BCG in the adjuvant formulation results in a positive body-weight development compared to living BCG. Furthermore, **fig. 2 shows that approx. 70% of the mice receiving heat-killed BCG together with the adjuvant formulation were still alive when the experiment ended in contrary to what was seen with the living BCG, where only 10% of the mice were alive. Example 2 and 3 support these findings, and further demonstrate the importance that the primary vaccination also is performed with inactivated BCG**.

In conclusion, Applicants most respectfully submit that one of ordinary skill in the art no motivation to combine the teachings of Youmans et al. with Schroder and even if he did he could not arrive at the present invention, namely that the use of inactivated M. Tuberculosis bacteria in a specific adjuvant would lead to a suitable immune response with the expectation of success achieved by the presently claimed invention

and set forth in the examples in the present specification. Accordingly, it is most respectfully requested that this rejection be withdrawn.

The rejection of newly submitted claims 38-45 under 35 U.S.C. 103(a) as unpatentable over Youmans et al. in view of Schroder is specifically traversed for the reasons set forth in the previous action and as stated above.

The method used for vaccinating a mammal against tuberculosis as now claimed includes the administration of a vaccine composition comprising the L3 adjuvant and inactivated mycobacterium. As describes above, Youmans et al. does not teach the use of adjuvants as beneficial, and furthermore, the method using inactivated *M. tuberculosis* cells provides very poor results. This would be considered by one of ordinary skill in the art as leading one away from the presently claimed invention as there would not be an expectation of success. Obvious to try is not the standard of obviousness under 35 USC 103.

The rejection of claims 11-37 under 35 U.S.C. 103(a) as unpatentable over Youmans et al. in view of Schroder and further in view of Van Nest et al. has been carefully considered but is most respectfully traversed for the reasons set forth in the previous Official Action and for the following reasons.

The Official Action rejects claims 11-37 (item 7) and claims 38-46 (item 8) as unpatentable over Youmans et al in view of Schroder and further in view of Van Nest et al. These rejections have been carefully considered but are most respectfully traversed. As discussed above, Applicants do not believe that a prima facie case of obviousness has been established for a person skilled in the art in view of Youmans in combination with Schroder. The Van Nest reference does not overcome the deficiencies of the primary and secondary reference.

Van Nest et al relates to the use of any metabolizable oil for use in an adjuvant composition. There is no mention of the use of the adjuvant claimed in Van Nest et al. together with inactivated cells from M. Tuberculosis bacteria. Furthermore, the only administration route mentioned is by injection (see column 14, lines 28-33). Accordingly, the combined teachings of the three documents do not fill the gap between the

combined teachings of Youmans et al and Schroder which in no way suggest any aspect of the presently claimed invention.

As discussed above and along the same line of arguments, a person skilled in the art would have no motivation to combine the teachings of Youmans and Van Nest et al. If the teachings of Schroder and Van Nest et al are combined a person skilled in the art could at the best arrive at an adjuvant of Schroder further containing a metabolizable oil, the adjuvant being in the form of an emulsion and suitable for injection. There is no indication in Van Nest et al that a metabolizable oil used in an adjuvant can be suitable for mucosal administration. Accordingly, Applicants most respectfully submit that the combined teachings of any of the Youmans et al and Schroder, Youmans et al and Van Nest, Schroder and Van Nest nor Youmans et al and Schroder and Van Nest et al will lead a person skilled in the art to the present invention. Accordingly, it is most respectfully requested that these rejections be withdrawn.

In view of the above comments and further amendments to the claims, favorable reconsideration and allowance of all of the claims now present in the application are most respectfully requested.

Respectfully submitted,

BACON & THOMAS, PLLC

By: Richard E. Fichter
Richard E. Fichter
Registration No. 26,382

625 Slaters Lane, 4th Fl.
Alexandria, Virginia 22314
Phone: (703) 683-0500
Facsimile: (703) 683-1080

REF:kdd
A02.wpd

May 12, 2004